

## PRODUCT MONOGRAPH

### **Pr NOCDURNA®**

#### **Desmopressin Orally Disintegrating Tablet**

**25 µg, 50 µg desmopressin (as desmopressin acetate)**

**Antidiuretic**

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# **NOCDURNA**

**(Desmopressin Orally Disintegrating Tablet)**

## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Non medicinal Ingredients</b>
Sublingual	Orally Disintegrating Tablets Female: 25 µg Male: 50µg	Gelatin, Mannitol, Citric Acid

### **INDICATIONS AND CLINICAL USE**

NOCDURNA is indicated for treatment of nocturia in adults with four or less nocturnal voids. An insufficient number of adults with more than four nocturnal voids were studied to allow a conclusion on the efficacy of NOCDURNA in these subjects.<sup>1, 2, 3, 4, 5,17, 24, 26, 27, 28, 29, 30, 31,32, 44</sup>

#### **Geriatrics:**

Clinical studies of desmopressin in the elderly at higher doses and with different dosage forms have shown an increased risk of hyponatremia with age and declining creatinine clearance.

Desmopressin acetate is known to be excreted by the kidney, and the risk of adverse reactions to desmopressin may be greater in patients with impaired renal function. Desmopressin is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50 mL/min).<sup>8</sup> [See Clinical Pharmacology and Contraindications]

Use of NOCDURNA requires careful fluid restriction to prevent possible prolonged fluid retention and subsequent hyponatremia. Fluid restriction should be discussed with the patient.<sup>35</sup> [See Warnings and Precautions]

## **Pediatrics:**

Although the efficacy and safety of desmopressin acetate for use in pediatric Primary Nocturnal Enuresis (PNE) have been established with other formulations of desmopressin acetate, NOCDURNA doses of 25 µg and 50 µg have not been studied in this population.

## **CONTRAINDICATIONS**

### **Hypersensitivity**

Hypersensitivity to desmopressin acetate or to any ingredient in the formulation or any component of NOCDURNA. For complete listing, see Dosage Forms, Composition and Packaging section of the Product Monograph.

### **Polydipsia**

Habitual or psychogenic polydipsia (fluid intake resulting in a urine production exceeding 40 mL/kg/24 hours).

### **Hyponatremia**

NOCDURNA is contraindicated in patients with hyponatremia or a history of hyponatremia.

### **Renal impairment**

NOCDURNA is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50 mL/min).<sup>8</sup>

### **Cardiac Insufficiency**

A history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics.

### **Syndrome of Inappropriate Antidiuretic Hormone Secretion**

NOCDURNA is contraindicated in patients with known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion.

## **Hematology**

Because of the risk of platelet aggregation and thrombocytopenia, the drug should not be used in patients with type IIB or platelet-type (pseudo) von Willebrand's disease.

## **Sodium Losing Conditions**

Existing medical conditions, which lead to sodium losing states such as nausea, bulimia, anorexia nervosa, chronic vomiting, diarrhea, adrenocortical insufficiency and salt losing nephropathies, are contraindicated for the use of desmopressin acetate.

## **WARNINGS AND PRECAUTIONS**

### **General**

#### **Fluid Intake**

Patients treated with diuretics for fluid retention should not be treated with desmopressin acetate.

#### **Fluid Restriction**

Fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration. Treatment without concomitant reduction of fluid intake may lead to prolonged fluid retention and/or hyponatremia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, weight gain, and in severe cases, convulsions). <sup>6</sup>

#### **Hyponatremia**

NOCDURNA is a potent antidiuretic that may lead to prolonged fluid retention and/or hyponatremia, especially during the initial days of treatment, in elderly patients and patients with serum sodium levels in the low range. Unless properly diagnosed and treated, hyponatremia can be life-threatening. One of the phase III studies (CS29) indicated that during treatment with NOCDURNA, 3.1% and 4.2% of hyponatremia cases were observed in female and male subjects respectively. Therefore, serum sodium should be in the normal range before starting treatment and overall fluid restriction is warranted in all patients. <sup>35</sup> Desmopressin treatment should be discontinued if serum sodium level falls below 125mmol/L

Men aged 65 years and older on NOCDURNA 50 µg should have their serum sodium monitored within 4-8 days after initiation and at one month of treatment. <sup>35</sup> [See Dosage and Administration]

Patients receiving NOCDURNA therapy may potentially develop symptomatic hyponatremia and experience the following signs or symptoms: headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, lethargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps, and abnormal mental status such as hallucinations, decreased consciousness, and confusion. Severe symptoms may include one or a

combination of the following: seizure, coma and/or respiratory arrest. However, patients with serum sodium concentration below normal range can be asymptomatic.<sup>35</sup>

### **Acute Illnesses**

Treatment with desmopressin should be interrupted during acute intercurrent illnesses characterized by fluid and/or electrolyte imbalance (such as systemic infections, fever, and diarrhea).

### **Drugs that Potentiate Inappropriate Antidiuretic Hormone Secretion**

Drugs that are known to induce syndrome of inappropriate antidiuretic hormone secretion may cause an additive antidiuretic effect leading to an increased risk of fluid retention/hyponatremia.

### **Cardiovascular**

The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible tachycardia and changes in blood pressure.

### **Genitourinary**

#### **Bladder Dysfunction and Outlet Obstruction**

Severe bladder dysfunction (i.e., neurological bladder dysfunction), outlet obstruction, low bladder capacity [such as overactive bladder (OAB) and benign prostate hyperplasia (BPH)], urological malignancies and gynecological abnormalities should be considered before starting treatment.

### **Renal**

Desmopressin is mainly excreted in the urine. A pharmacokinetic study conducted in healthy volunteers and patients with mild, moderate, and severe renal impairment (n=24, 6 subjects in each group) receiving single-dose desmopressin acetate (2 µg) injection demonstrated a difference in desmopressin terminal half-life. Terminal half-life significantly increased from 3 hours in healthy volunteers to 9 hours in patients with severe renal impairment.<sup>8</sup>

Desmopressin is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50 mL/min).<sup>8</sup> [See Contraindications]

### **Respiratory**

Desmopressin acetate should be used with caution in patients with cystic fibrosis because these patients are prone to developing hyponatremia.

### **Other Conditions**

Uncontrolled diabetes mellitus, uncontrolled hypertension, obstructive sleep apnea, hepatic and biliary disease.

## **Special Populations**

### **Pregnant Women**

No controlled studies in pregnant women have been carried out. However, as with all medication used during pregnancy, the physician should weigh possible therapeutic advantages against potential risks in each case.

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus <sup>22</sup> as well as data on exposed pregnancies in women with bleeding complications (n = 216) <sup>38</sup> indicate no adverse effects of desmopressin on pregnancy or on the health of the fetus or newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Nevertheless, caution should be exercised when prescribing to pregnant women. [See Toxicology]

### **Nursing Women**

There have been no controlled studies in nursing mothers. Results from analysis of milk from nursing mothers receiving high doses of desmopressin (300 µg intranasal), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.<sup>44</sup>

### **Pediatrics**

Although the efficacy and safety of desmopressin acetate in pediatrics Primary Nocturnal Enuresis (PNE) have been demonstrated with other desmopressin acetate formulations<sup>32</sup> NOCDURNA doses of 25 µg and 50 µg have not been studied in this population.

### **Geriatrics**

Clinical studies of desmopressin in the elderly at higher doses and with different dosage forms have shown an increased risk of hyponatremia with age and declining creatinine clearance. Desmopressin acetate is known to be excreted by the kidney, and the risk of adverse reactions to desmopressin may be greater in patients with impaired renal function. Desmopressin is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50 mL/min). <sup>33</sup> [See Clinical Pharmacology and Contraindications]

## **Monitoring and Laboratory Tests**

Prior to treatment with NOCDURNA, all patients should have serum sodium within the normal range.

### **Men 65 years of age and older**

For men 65 years and older, additional serum sodium monitoring is warranted within 4-8 days after initiation and at one month of treatment NOCDURNA should be discontinued if serum sodium falls below normal range.<sup>3,4,5</sup>[See Contraindications and Warnings and Precautions]

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The safety analysis is derived from the following Phase 3 studies: CS29, CS31 and CS41.

Clinical trials CS29 and CS41 were placebo controlled, whereas CS31 and CS41 part II were open label extension trials of CS29 and CS41 part I respectively.

In CS29 (evaluating NOCDURNA 10, 25, 50, 100 µg and placebo in males and females), the most common ADR for NOCDURNA by MedDRA preferred term was dry mouth (26.7%);. It should be noted that in this study subjects were specifically prompted about dry mouth; furthermore, the incidence of dry mouth was rather similar in the desmopressin NOCDURNA (24%) and placebo (25%) treatment groups.<sup>3</sup>

In CS41 Part I (evaluating NOCDURNA 50, 75 µg and placebo in males), the most common ADR overall by MedDRA preferred term was dry mouth (3.1%), headache (2.9%) and hyponatremia (2.1%).<sup>5</sup>

### **Clinical Trial Adverse Drug Reactions**

#### **CS29 and CS31**

CS29 was conducted in 2 parts. Part I was a double-blind, placebo-controlled, multi-center, randomized, parallel-group study investigating the efficacy and safety of 4 doses of NOCDURNA (10, 25, 50, and 100 µg). Subjects on active drug continued into CS29 Part II for 1 to 6 months and those on placebo were blindly randomized to an active dose. Subjects enrolled in CS29 Part II were eligible for study CS31, a long-term, open-label efficacy and safety extension. In CS31, subjects on the 10 µg dose were re-randomized to 25, 50 or 100 µg.<sup>3,4</sup>

A total of 778 subjects (639 CS29 Part 1; 139 re-randomized placebo) with nocturia were exposed to NOCDURNA in these Phase 3 clinical trials. A total of 367 subjects were treated for at least 1 year, of which 97 subjects were on the highest dose of 100 µg.<sup>3</sup>

A summary of treatment-emergent adverse events reported by >1.0% of subjects in the NOCDURNA 25 or 50 µg during Part I of CS29 is presented by descending order of overall frequency in Table 1.<sup>3</sup>

<b>Table 1. Treatment-Emergent Adverse Events Considered Possibly or Probably Related to Study Drug Reported by at Least 1.0% of Subjects (CS29 Part I)</b>				
	<b>Females</b>		<b>Males</b>	
<b>MedDRA Preferred Term</b>	<b>Placebo (N=67) n (%)</b>	<b>NOCDURNA 25 µg (N=96) n (%)</b>	<b>Placebo (N=93) n (%)</b>	<b>NOCDURNA 50 µg (N=118) n (%)</b>
Any ADR	21 (31.3%)	40 (42.6%)	26 (28.0%)	44 (37.3%)
Dry mouth	17 (25.4%)	23 (24.0%)	21 (22.6%)	28 (23.7%)
Headache	2 (3.0%)	1 (1.0%)	2 (2.2%)	6 (5.1%)
Hyponatraemia	0	3 (3.1%)	1 (1.1%)	5 (4.2%)
Dizziness	0	2 (2.1%)	0	4 (3.4%)
Nausea	0	3 (3.1%)	0	2 (1.7%)
Blood sodium decreased	1 (1.5%)	2 (2.1%)	0	4 (3.4%)
Diarrhoea	0	1 (1.0%)	1 (1.1%)	3 (2.5%)
Fatigue	0	0	1 (1.1%)	2 (1.7%)
Micturition urgency	0	2 (2.1%)	1 (1.1%)	0
Muscle spasm	0	2 (2.1%)	0	0

ADR = (adverse drug reaction) AE assessed by the Investigator as possibly/probably related to study drug

Cross-reference: [\[Table 14.6.3.2\] ISS](#)

As shown in Table 2, treatment-emergent adverse events reported by >5.0% of subjects in the NOCDURNA 25 and 50 µg groups were dry mouth, diarrhea and headache. It should be noted that subjects were specifically queried about dry mouth; therefore, it was not unexpected that the incidence of dry mouth was generally similar in the NOCDURNA (31.3-33.3%) and placebo (23.7-32.8.0%) treatment groups. In contrast, during CS31 open-label extension study and CS41, subjects were not queried about dry mouth, and the reported incidence of dry mouth was about 3%.<sup>3,4</sup>

**Table 2: Summary of Common (>5.0% of Subjects in Any Treatment Group) Treatment-Emergent Adverse Events (CS29 Part I)**

	Females		Males	
	Placebo (N=67) n (%)	NOCDURNA 25 µg (N=67) n (%)	Placebo (N=93) n (%)	NOCDURNA 50 µg (N=78) n (%)
<b>Gastrointestinal Disorders</b>				
Dry mouth	22 (32.8%)	21 (31.3%)	22 (23.7%)	26 (33.3%)
Diarrhea	0	3 (4.5%)	2 (2.2%)	4 (5.1%)
<b>Nervous System Disorders</b>				
Headache	4 (6.0%)	1 (1.5%)	5 (5.4%)	4 (5.1%)

Cross reference: [\[14.7.3.2\] CS31 CTR](#)

## CS41

The safety of NOCDURNA in males was further investigated in a multicenter Phase 3 trial (CS41) consisting of 2 parts. Part I was a double-blind, randomized, placebo-controlled, parallel-group 3-month period designed to evaluate the clinical effect and safety of two doses of NOCDURNA for treatment of nocturia in adult males. A total of 395 subjects were randomized to 1 of 3 treatment groups (NOCDURNA 75 µg, NOCDURNA 50 µg, or placebo). After the first 3 months of treatment, subjects were allowed to switch to desmopressin 100 µg for a period of 1 month for further evaluation of safety in an open-label extension phase (Part II).<sup>5</sup>

### CS41 Part I

A summary of treatment-emergent adverse drug reactions reported by >1.0% of subjects in the NOCDURNA 50 µg during Part I of CS41 is presented in Table 3.<sup>5</sup>

**Table 3: Treatment-Emergent Adverse Drug Reactions Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set) – CS41 Part I**

System Organ Class MedDRA Preferred Term	Placebo (N=143) n (%)	NOCDURNA 50 µg (N=119) n (%)
<b>Gastrointestinal Disorders</b>		
Dry mouth	7 (5%)	4 (3%)
<b>Injury, Poisoning and Procedural Complications</b>		
Medication error	1 (<1%)	2 (2%)
<b>Metabolism and Nutrition Disorders</b>		
Hyponatremia	0	3 (3%)
<b>Nervous System Disorders</b>		
Headache	2 (1%)	4 (3%)
Dizziness	1 (<1%)	2 (2%)
<b>Psychiatric Disorders</b>		
Abnormal dreams	0	2 (2%)

ADR = adverse drug reaction; an AE assessed by the Investigator as possibly/probably related to study drug

Cross-reference: [\[Table 7.1.10\] CS 41 CTR](#)

## CS41 Part II

In CS41 part II patients were treated, in an open-label, to a much higher dose of 100 µg for a month in order to collect safety data at a higher dose.<sup>5</sup> No safety concerns and unexpected adverse drug reaction were reported. In CS41 part II, 1% subjects experienced hyponatraemia and diarrhea.

### Long Term Exposure Safety Data

In CS29 Part II and CS31 subjects were exposed for up to two years at doses ranging from 25 µg to 100 µg.<sup>3,4</sup> No safety concerns and unexpected adverse drug reaction were reported even at high doses (upto 100 µg). Dry mouth with an incidence of 3% remained the most frequent reported adverse event in the CS31. The other AEs had an incidence of <1%.

The long-term studies CS29 Part II and CS31 confirmed that the NOCDURNA is a safe and well tolerated drug.<sup>3,4</sup>

### Abnormal Hematologic and Clinical Chemistry Findings

### Laboratory Values Over Time

Minor mean changes from baseline to the last visit were observed in hematology, clinical chemistry and urinalysis in all treatment groups. None of the mean changes or mean percentage changes was considered to be clinically meaningful.<sup>3,4,5</sup>

## **Post-Market Adverse Drug Reactions**

The following adverse reactions have been identified during post approval use of desmopressin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Desmopressin has been marketed worldwide since 1972 in several formulations, including intranasal, intravenous, and oral formulations for the treatment of diabetes insipidus and primary nocturnal enuresis. The other oral formulations are available at much higher doses than NOCDURNA. The most frequent reported adverse reactions on alternate oral formulations are as follows:

### **Electrolytes**

Hyponatremia/decreases serum sodium

### **Gastrointestinal Disorders**

Abdominal pain, vomiting, nausea

### **Nervous System**

Headache, convulsions

### **Skin**

Rash/urticaria

### **Sensitivity/Resistance**

Lack of effect

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

#### **Drugs that potentiate inappropriate anti-diuretic hormone secretion**

Drugs that are known to induce inappropriate antidiuretic hormone secretion may cause an additive antidiuretic effect leading to an increased risk of inappropriate fluid retention/hyponatremia.

#### **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

NSAIDs may induce additional fluid retention/hyponatremia.

## **Hepatic Metabolism**

It is unlikely that NOCDURNA will interact with drugs affecting hepatic metabolism (i.e. CYP 450 system), since desmopressin has been shown not to undergo significant liver metabolism during in vitro studies with human microsomes.<sup>33</sup> However, formal *in vivo* interaction studies have not been performed with NOCDURNA.

## **Drug-Food Interactions**

No food interaction study was conducted with the NODCURNA formulation. It has been previously shown that intake of a standardized meal with desmopressin tablets has no effect on pharmacodynamic parameters (urine production and osmolality) despite some pharmacokinetic influence. The fact that sublingually administered NOCDURNA is absorbed initially in the oral mucosa, pharynx and oesophagus implies that it is even less likely that food intake will influence its absorption.<sup>34</sup> Furthermore, the intended bedtime administration of desmopressin is not typically the time of meal. Therefore, it is very unlikely that any clinically significant drug-food interaction exists with sublingual administration of NOCDURNA.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

#### **Fluid Restriction**

Patients should be instructed to limit fluid intake to a minimum from 1 hour before until 8 hours after administration. Overall fluid restriction should be observed. Treatment without concomitant reduction of fluid intake may lead to fluid retention and/or hyponatremia with or without accompanying warning signs and symptoms.

#### **Serum Sodium Monitoring**

All patients should receive a baseline serum sodium test to confirm serum sodium is in normal range before treatment initiation. Remind patients over age 65 of the importance of adhering to the recommended sodium monitoring schedule. NOCDURNA should be discontinued if serum sodium is below normal range.<sup>3, 4, 5</sup>

#### **Hyponatremia**

Patients should be informed about the following signs and symptoms associated with hyponatremia: headache, nausea/vomiting, weight gain, restlessness, fatigue, tiredness, disorientation, muscle weakness, muscle spasms or cramps, and confusion. Desmopressin acetate treatment should be discontinued if serum sodium levels falls below 125mmol/L.

#### **Acute Illness or Concomitant Medications**

Patients should be informed that treatment should be stopped during acute intercurrent illnesses that can lead to fluid and/or electrolyte imbalance such as systemic infections (flu), fever, or chronic diarrhea. Caution patients about concomitant medications that can lead to hyponatremia.

### **Recommended Dose and Dosage Adjustment**

Women	25 µg daily at bedtime administered sublingually
Men < 65	50µg daily at bedtime administered sublingually
Men $\geq$ 65	50µg daily at bedtime administered sublingually with additional serum sodium monitoring o within 4-8 days after initiation and at one month of treatment

### **Missed Dose**

If the patient misses a dose, the patient should be advised not to take the missed dose.

### **Administration**

NOCDURNA is an orally disintegrating tablet taken sublingually.

Restricted fluid intake is recommended a few hours before administration, especially one hour before, and until the next morning (at least 8 hours) after administration.

### **OVERDOSAGE**

Recommended doses of NOCDURNA should not be exceeded. Overdose leads to a prolonged duration of action with an increased risk of prolonged fluid retention and hyponatremia. Signs of overdose may include nausea, headache, drowsiness, confusion, and rapid weight gain due to fluid retention. [See Warnings and Precautions]

In case of overdose, therapy should be discontinued. There is no known specific antidote for desmopressin. Symptomatic patients should be observed and cases of hyponatremia should be treated appropriately.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

The antidiuretic effects of desmopressin are mediated by stimulation of V<sub>2</sub>-receptors thereby increasing water re-absorption in the kidney, and hence reducing urine production. Stimulation of V<sub>2</sub>-receptors may also cause an increase in the levels of blood coagulation factors, factor VIII and von Willebrand factor, but this effect occurs at higher doses of desmopressin than those required for inducing antidiuresis.<sup>42</sup>

### **Pharmacodynamics**

NOCDURNA contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

In study CS29, the weight-corrected NOCDURNA dose that induced 50% maximum achievable drug effect on nocturnal urine volume differed significantly between females and males. The estimated exposure for males was 2.7 fold (95% CI: 1.3-8.1) higher than the value for females to obtain an identical dynamic effect, corresponding to higher desmopressin sensitivity among females.<sup>3</sup>

Gender and age appear to have a dose-dependent effect on hyponatremia. The incidences of hyponatremia rise with increasing dose and with increasing age.

### **Pharmacokinetics**

#### **Absorption**

The overall mean absolute bioavailability of desmopressin orally disintegrating tablets administered sublingually from earlier dose-ranging studies of doses of 200, 400 and 800 is 0.25% with a 95% confidence interval of 0.21 – 0.31%.<sup>9</sup> Desmopressin exhibits a moderate-to-high variability in bioavailability, both within and between subjects.<sup>10</sup> Desmopressin orally disintegrating tablets show dose linearity regarding AUC and C<sub>max</sub> in the range of 60 to 240.<sup>7</sup> However, the bioavailability of doses below 60 has not been evaluated.

#### **Distribution:**

The distribution volume of desmopressin after intravenous administration is 33 L.

## **Metabolism:**

Desmopressin did not show any effect on any of the nine CYP 450 subtypes. *In vivo* drug-drug interactions based on activation or inhibition of CYP P450 are therefore very unlikely. <sup>-20</sup>

## **Excretion:**

Desmopressin is mainly excreted in the urine. After intravenous injection, 52% of the dose could be recovered in the urine within 24 hours as unchanged desmopressin. The geometric mean terminal half-life is 2.8 (CV = 24%) hours.<sup>8</sup>

Terminal half-life significantly increases in patients with severe renal impairment (see Warnings and Precautions).<sup>8</sup>

## **Special Populations and Conditions**

### **Geriatric**

The pharmacokinetics of desmopressin acetate in the nocturia population does not differ from those in healthy subjects. A pooled data analysis demonstrated no significant correlation between age and pharmacokinetics, and no gender-related difference in AUC<sub>inf</sub> could be found. In very elderly patients, a decrease in the renal elimination of desmopressin could be expected.<sup>34</sup>

Use of NOCDURNA requires careful fluid restriction to prevent possible prolonged fluid retention and subsequent hyponatremia. Fluid restriction should be discussed with the patient [See Warnings and Precautions and Gender and Age Effects].

### **Gender and Age Effect**

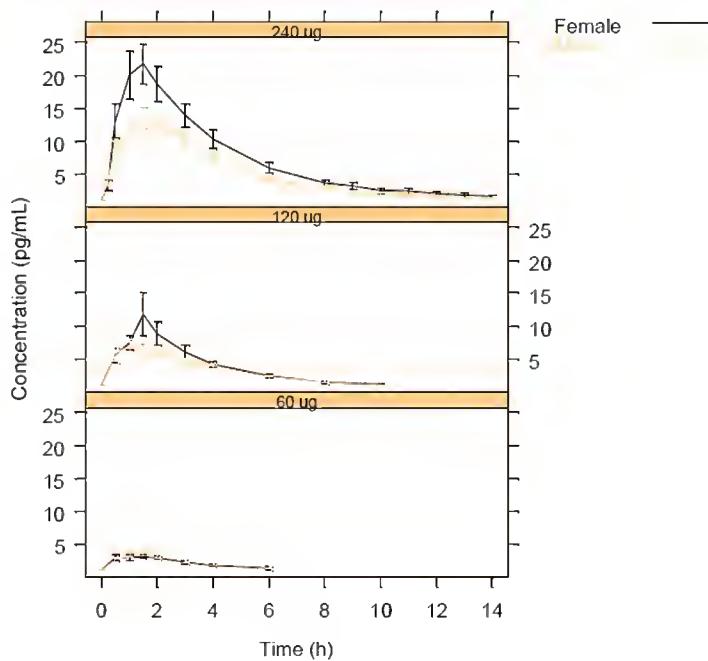
A two part study involving single oral dosage with 400 µg desmopressin (Part A) and a randomized, placebo-controlled, 2 way crossover evaluation involving treatment with 400 µg desmopressin or placebo for 3 consecutive nights with a 7-14 day washout period showed that the pharmacokinetic parameters in elderly (>65 years) nocturic subjects did not differ from those in healthy subjects. A gender-related difference in the extent but not in the rate of absorption was observed.<sup>11</sup> A subsequent pooled data analysis of several clinical studies did not confirm this difference. The linear relationship between plasma desmopressin concentrations at 2-3 hours post-dose and AUC<sub>inf</sub> in these subjects suggests that plasma desmopressin concentrations at 2 (or 3) hours can be used as an accurate predictor of AUC<sub>inf</sub> in elderly subjects with nocturia.

The low level of absorption of desmopressin following oral administration means that a high level of variability may be expected. A study evaluating intra and inter individual variation in pharmacokinetics of desmopressin after three administration in an oral lyophilisate to healthy non-smoking volunteers showed no gender differences in intra and inter-subject variability in AUC- $\infty$  AUC, or C<sub>max</sub>. After multiple (3) doses of desmopressin Melt at 200 µg, the PK parameters did not differ statistically significantly after each dose.<sup>10</sup>

The large Phase 3 study with desmopressin Melt CS029 is the first to show a clear gender difference in the effect of desmopressin on nocturnal urine volume. A further analysis was performed on the data obtained from nocturia patients in this study, together with single-dose pharmacokinetic data from healthy subjects in a three-period crossover study comparing the exposure of oral lyophilisate containing 60, 120 and 240 µg desmopressin in 24 non-smoking subjects<sup>6</sup> and an open-labeled, randomized, two period crossover study investigating the relative bioavailability of two single doses of the currently marketed MINIRIN Tablets (2 x 200 µg) and a single dose of desmopressin administered as a new orodispersible tablet (240 µg).<sup>6</sup>

Mean desmopressin concentration profiles are shown by dose and gender in Figure 1. Age and gender were found not to be statistically significant while weight was significant with respect to  $\log(C_{max})$  and borderline significant with respect to  $\log(AUC)$ . Gender differences in drug exposure were not statistically significant when adjusting for body weight.

**Figure 1 Modelling Analysis: Mean Desmopressin Concentration by Dose and Gender**



The incidence of hyponatremia increased with increasing doses of NOCDURNA. In CS29 and CS31, hyponatremia referred to serum sodium below 130 mmol/L, and patients continued treatment unless serum sodium fell below 125 mmol/L. No female subject who received NOCDURNA 25 µg had serum sodium levels below 125 mmol/L and none of these subjects discontinued therapy due to hyponatremia. No males under 65 years of age had serum sodium levels below 125 mmol/L. During CS29, among males  $\geq 65$  years of age, 2 who received NOCDURNA 100 µg and 1 who received 50 µg NOCDURNA had serum sodium levels fall below 125 mmol/L; all 3 subjects were discontinued, 2 due to “hyponatremia” and 1 due to “blood sodium decreased.” Minimum post

baseline serum sodium levels by age groups in females treated with NOCDURNA 25 µg and males treated with NOCDURNA 50 µg is presented by age group for CS29 and CS31 in Table 4.<sup>3, 4</sup>

**Table 4 Minimum Post-Baseline Serum Sodium Levels by Age Group in Females Treated with NOCDURNA 25 µg and Males treated with NOCDURNA 50µg (Overall Safety population CS29+CS31)**

Serum Sodium (mmol/L)	NOCDURNA 25 µg for Females		NOCDURNA 50 µg for Males	
	<65 years (N=59)	≥65 years (N=37)	<65 years (N= 53)	≥65 years (N=65)
Observed N*	59 (100%)	37 (100%)	52 (98.1%)	65 (100%)
≥135	48 (81.4%)	27 (73.0%)	37 (69.8%)	33 (50.8%)
130-134	10 (16.9%)	6 (16.2%)	15 (28.3%)	21 (32.3%)
125-129	1 (1.7%)	4 (10.8%)	0	10 (15.4%)
<125	0	0	0	1( 1.5%)

Cross reference: [\[Table 14.8.1.9 \]CS31 CTR](#) – Overall safety CS29 and CS31

\*Number of subjects with data

## CS41 Part I

During CS41 Part I, 4 males who received NOCDURNA 75 µg and 2 who received NOCDURNA 50 µg had serum sodium less than or equal to 125 mmol/L; all 6 subjects were discontinued, 5 due to “hyponatremia” and 1 due to “dizziness”. No males <65 years of age who received NOCDURNA 50 µg and one male who received NOCDURNA 75 µg had serum sodium ≤125 mmol/L. Minimum post baseline serum sodium levels in males who received NOCDURNA 50 µg is presented by age group for CS41 Part I in Table 5.<sup>5</sup>

**Table 5: Minimum Post-Baseline Serum Sodium Levels by Age Group in Males Treated with NOCDURNA 50µg (CS41 Part I)**

Serum Sodium (mmol/L)	NOCDURNA 50 µg (N=119)	
	Age <65 (N=62)	Age ≥65 (N=57)
≥ 135	60 (97%)	48 (84%)
130-134	2 (3%)	7 (12%)
126-129	0	0
≤125	0	2 (4%)

Cross reference: [Table 7.1.1.5 and 7.1.1.6 ] CS41 CTR

Due to the rare cases of serum sodium levels ≤125 mmol/L in males ≥65 years who received NOCDURNA 50 µg in the Phase 3 trials, serum monitoring is warranted in this group.<sup>3, 4, 5</sup>

## STORAGE AND STABILITY

Store at 25°C; excursions permitted to 15 – 30°C. Keep in original package to protect from moisture and light. Use immediately upon opening individual tablet blister.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

NOCDURNA is an orally disintegrating tablet containing desmopressin acetate equivalent to 25 or 50 µg of desmopressin as free base. The inactive ingredients are gelatin, mannitol, and anhydrous citric acid.

NOCDURNA 25 µg is a white, round, orally disintegrating tablet with “25” on one side.

NOCDURNA 50 µg is a white, round, orally disintegrating tablet with “50” on one side.

NOCDURNA Initiation Pack for Men  $\geq$  65 Years of Age is packaged as a unit dose blister (4 units per box)

NOCDURNA is packaged as a unit dose blister, 10 units per blister pack, 3 blister packs (30 unit doses) per box.

#### **SPECIAL HANDLING INSTRUCTIONS**

No special requirement

## PART II : SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proprietary Name: Desmopressin Acetate

Chemical names: 1-Desamino-8-D-arginine vasopressin acetate trihydrate

1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate

Molecular formula and molecular mass:

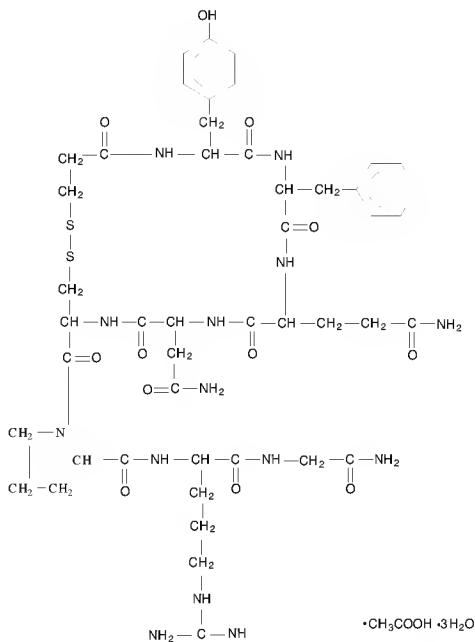
$C_{48}H_{74}N_{14}O_{17}S_2$  (acetate trihydrate)

MW = 1183.2

$C_{46}H_{64}N_{14}O_{12}S_2$  (free base)

MW = 1069.2

Structural formula:



## Physicochemical Properties:

Desmopressin acetate is a white lyophilized powder which is soluble in water, methanol, ethanol, and acetic acid, and sparingly soluble in chloroform and ethyl acetate. An aqueous solution of 1 mg/mL at 24°C has a pH of 4.8.

## CLINICAL TRIALS

### NOCDURNA 25 µg in Females

The safety and efficacy of NOCDURNA 25 µg in females were evaluated in two Phase 3 studies, CS29 and CS31. CS29 was conducted in 2 parts. Part I was a double-blind, placebo-controlled, multi-center, randomized, parallel-group study investigating the efficacy and safety of 4 doses (10, 25, 50, and 100 µg) of NOCDURNA administered at bedtime for 28 days for the treatment of nocturia in male and female adults. A total of 757 subjects were included in the ITT population. Subjects on active drug continued into CS29 Part II for 1 to 6 months and those on placebo were blindly randomized to an active dose.<sup>3,4</sup>

The ITT population (n=757) across all treatment arms had an overall median age of approximately 64 years (range 20 to 89 years). The majority of subjects participating were Caucasian. The ethnic/racial distribution was 80.4% Caucasian, 15.3% black, 2.1% Asian, and 1.8% others. Subjects with following conditions were excluded from the trials: Neurogenic bladder dysfunction, severe OAB and BPH (low bladder capacity), urological malignancies gynaecological abnormalities, pregnancy, uncontrolled hypertension, uncontrolled diabetes mellitus, low baseline serum sodium, diabetes insipidus, SIADH secretion and polydipsia.<sup>3</sup>

Durability of effect was assessed and confirmed for up to 96 weeks during CS29 Part II and the open-label extension study CS31. A total of 601 NOCDURNA-treated subjects (excluding placebo subjects) were included in the ITT population of CS29 and CS31 combined.<sup>3,4</sup>

The co-primary endpoints, measured from baseline to the final visit in CS29 Part I (Day 28), were the change in the mean number of nocturnal voids and the proportion of subjects with >33% reduction in the mean number of nocturnal voids. In addition to these co-primary endpoints, the change from baseline in the initial period of undisturbed sleep and nocturnal urine volume were also evaluated in CS29 Part I as well in the durability studies, CS29 Part II and CS31.<sup>3,4</sup>

At Day 28 the difference in the mean number of nocturnal voids and the proportion of subjects with >33% reduction in the mean number of nocturnal voids was statistically significant, favoring NOCDURNA 25 µg over placebo. The mean reductions in nocturnal voids were 1.22 voids in females receiving NOCDURNA 25 µg versus 0.88 voids for placebo (p=0.0200). The 33% responder rates were 62% in females receiving NOCDURNA 25 µg versus 42% for placebo (p=0.0197). Statistical analyses of the efficacy data, based on a linear model for change from baseline and logistic regression for 33% responder, with adjustment for nocturnal polyuria status, age group and baseline number of voids, for females treated with NOCDURNA 25 µg are presented in Table6.<sup>3</sup>

**Table 6. Primary Efficacy results for Females treated with NOCDURNA 25 µg at Day 28 (CS29 Part I, ITT Analysis Dataset)**

Co-primary efficacy endpoints	NOCDURNA 25 µg N=65	Placebo N=66
<b>Number of nocturnal voids</b>		
Mean change from baseline (SD)	-1.22 (1.060)	-0.88 (1.008)
Adjusted mean treatment difference <sup>1</sup> (95% CI) P=0.0200	-0.397 (-0.731, -0.063)	
<b>33% responder status</b>		
Proportion of patients achieving 33% reduction from baseline in mean no. of nocturnal voids	62%	42%
Odds Ratio <sup>2</sup> (95% CI) p=0.0197	2.344 (1.154, 4.848)	

SD = standard deviation, CI = confidence interval

1 ANCOVA of change from baseline at Day 28, adjusted for age stratification group (<65, >=65 years), absence/presence of nocturnal polyuria , and baseline nocturnal voids

2 Logistic regression of responder status at Day 28, adjusted for age stratification group (<65, >=65 years), absence/presence of nocturnal polyuria , and baseline nocturnal voids

Cross reference: [\[Table 14.3.1.13, 14.3.3.13, 14.3.4.13 and 14.3.6.13\]](#) ISE

Durability of effect was indicated during long-term treatment. The primary efficacy results that had been observed in CS29 Part I were maintained, sometimes improved, with continued NOCDURNA treatment in CS29 Part II and CS31 (Table7).<sup>3, 4</sup>

**Table 7: Change from Baseline in Mean Number of Nocturnal Voids and Proportion of Subjects with >33% Reduction in Mean Number of Nocturnal Voids in Females Receiving Long-term Treatment with NOCDURNA 25 µg (CS29 Part II, CS31)**

Endpoints	Mean Change in Nocturnal Voids Mean ( SD)	33% Responder Rate
28 Weeks	(N=29) -1.78 (1.138)	(N=29) 24 (83%)
52-56 Weeks	(N= 40) -1.74 (1.126)	(N= 40 ) 35 ( 87.5%)
72-76 Weeks	(N=36) -1.99 (1.235)	(N=36) 29 (80.6%)
92-96 Weeks	(N=32) -1.82 (1.068)	(N=32) 24 (75.0%)

Cross reference : [Table 14.5.1.2.3 and 14.5.2.2.3] CS31 CTR

In general, the initial period of undisturbed sleep increased in all treatment groups throughout study duration. Mean increases in the initial period of undisturbed sleep observed in CS29 Part I continued beyond 4 weeks. After 1 year of treatment, the mean initial period of undisturbed sleep among females increased by approximately 2.5 hours in the NOCDURNA 25 µg group. After 92-96 weeks of treatment, the mean initial period of undisturbed sleep increased by approximately 3.3 hours, giving an average first uninterrupted sleep time of approximately 4.9 hours.<sup>4</sup>

## NOCDURNA 50 µg in Males

The safety and efficacy of NOCDURNA 50 µg in males were evaluated in the Phase 3 study, CS41. CS41 was a double-blind, placebo-controlled, multicenter, randomized trial consisting of 2 parts. Part I was a double-blind, randomized, placebo-controlled, parallel-group 3-month period designed to evaluate the clinical effect and safety of two doses of NOCDURNA for treatment of nocturia in adult males. A total of 395 subjects were randomized to 1 of 3 treatment groups (NOCDURNA 75 µg, NOCDURNA 50 µg, or placebo). After the first 3 months of treatment, all subjects switched to desmopressin 100 µg for a period of 1 month for further evaluation of safety in an open-label extension phase (Part II).<sup>5</sup>

Randomisation was stratified by age (< 65 years, ≥ 65 years). The mean age was 60.6 years (median age: 64 years), and age ranged from 20 to 87 years. The majority of subjects participating were Caucasian. The ethnic/racial distribution was 81% Caucasian, 17% black, 2 % Asian, and <1% others.<sup>5</sup>

The co-primary endpoints were the change from baseline in the mean number of nocturnal voids and the proportion of subjects with >33% reduction from baseline in the mean number of nocturnal voids. Secondary endpoints included change from baseline in the initial period of undisturbed sleep and in nocturnal urine volume. Statistically significant differences, favoring both NOCDURNA 50 µg and 75 µg, were observed in these primary and secondary endpoints.<sup>5</sup>

At each visit (Week 1, Month 1, Month 2, and Month 3) the differences in the mean number of nocturnal voids were statistically significant, favoring NOCDURNA 50 µg over placebo. The mean (adjusted) reductions in nocturnal voids during 3 months were 1.25 voids with NOCDURNA 50 µg and 0.88 voids with placebo (p=0.0003).<sup>5</sup>

At each visit, the proportions of 33% responders were greater in males receiving NOCDURNA 50 µg compared to placebo. The (adjusted) odds of achieving a >33% responder status during the 3 months of treatment, as compared to placebo, was greater with NOCDURNA 50 µg (OR=1.98, p=0.0009). At Month 3, the 33% responder rate for NOCDURNA 50 µg was 67%.<sup>5</sup>

Statistical analyses of the efficacy data for males treated with NOCDURNA 50 µg are presented in Table 8.<sup>5</sup>

**Table 8. Primary Efficacy results for Males treated with NOCDURNA 50 µg during 3 months of treatment (CS41, Part I Full Analysis Set)**

Difference average over 3 months	NOCDURNA 50 µg N=119	Placebo N=142
<b>Co-primary efficacy endpoints</b>		
<b>Number of nocturnal voids</b>		
Baseline mean (SD)	2.88 (0.864)	2.90 (0.807)
Adjusted mean change from baseline <sup>1</sup>	-1.25	-0.88
Adjusted mean treatment difference <sup>1</sup> (95% CI)	-0.37 (-0.57, -0.17) p=0.0003	
<b>33% responder status</b>		
Adjusted probability of achieving 33% reduction from baseline in mean no. of nocturnal voids	0.67	0.50
Odds Ratio <sup>2</sup> (95% CI)	1.98 (1.32, 2.96) p=0.0009	

SD = standard deviation, CI = confidence interval

1 Repeated measures ANCOVA of change from baseline at Week 1, Month 1, Month 2 and Month, Adjusted for Age stratification factor (<65, >=65 years), visit, and baseline nocturnal voids

2 GEE Method for 33% responder status at Week 1, Month 1, Month 2 and Month 3. Adjusted for Age stratification factor (<65, >=65 years), visit, and baseline nocturnal voids

Cross reference: [\[Table 6.1.1.1, and 6.1.1.2\] CS41 CTR](#)

The initial period of undisturbed sleep increased throughout study duration. At 3 months, mean increase in the initial period of undisturbed sleep was approximately 112 minutes (p = 0.0064) in the NOCDURNA 50 µg group, giving an average first uninterrupted sleep time of approximately 4.3 hours.<sup>5</sup> The mean increase in the initial period of undisturbed sleep in the placebo group was approximately 73 minutes, giving an average first uninterrupted sleep of approximately 3.6 hours. The decrease in Nocturnal Urine Volume with 50 µg NOCDURNA was -209 mL, a 78 mL larger volume decrease than in the placebo group (p = 0.0086).

## QoL Responder Analysis

For the QoL assessments, pooled treatments for all subjects compared changes in key clinical endpoints between responders and non-responders. Two criteria were used to define responders. reduction of  $\geq 2$  nocturnal voids from baseline to Month 3 and increase of  $\geq 2$  hours in time to first nocturnal void from baseline to Month 3. For both definitions of responders, mean improvement (higher numbers) in NQoL scores was statistically significantly greater in subjects from pooled treatment groups who responded than in non-responders. Mean changes in quality of life, as measured by the global QoL score, bother/concern domain, and sleep/energy domain, are summarized longitudinally in Table 9.

**Table 9: Exploratory Efficacy Endpoints NQoL NOCTURIA (Longitudinal Analysis –Full Analysis Set**

Responder vs. Non-responder		
<b>N-QoL</b>		
<i>Responder Criteria: <math>\geq 2</math> voids reduction from baseline</i>	Difference in Adjusted Means [ 95% CI ]	P-value
Global Quality Score	5.73 [ 2.58; 8.87 ]	0.0004
Bother/Concern Domain	9.60 [ 6.04; 13.15 ]	<.0001
Sleep/Energy Domain	9.26 [ 5.64; 12.88 ]	<.0001
<i>Responder Criteria: <math>\geq 2</math> hrs increase in time to first void</i>	4.51 [ 1.60; 7.43 ]	0.0003
Global Quality Score	9.06 [ 5.80; 12.33 ]	<.0001
Bother/Concern Domain	8.63 [ 5.31; 11.95 ]	<.0001
Note: N-QoL is a scale of 0-100. Increased score means improved QoL		

## Treatment change in Mean Nocturia Quality of Life (NQoL) Scores

Post-hoc longitudinal analyses (repeated measures ANCOVA adjusting for baseline as a covariate and age stratification factor, treatment, visit, and treatment-by-visit interaction term as factor) were conducted to investigate the treatment effect of desmopressin versus placebo on the change from baseline in N-QoL domain scores and total score. Results for CS41 are shown in Table 10.

**Table 10: Adjusted treatment differences in mean change from baseline in N-QoL domain scores at Month 3 including treatment-by-visit interaction term (FAS using repeated measures ANCOVA)**

	Adjusted Means		Difference in Adjusted Means		
	Desmopressin	Placebo	Treatment Contrast	95% CI	p-value
<b>CS41</b>	N=103	N=127			
<b>Total Score (BC+SE)</b>	18.37	13.88	4.49	[0.24, 8.74]	<b>0.0385*</b>
<b>Bother/Concern Domain</b>	18.13	15.2	2.92	[-1.58, 7.42]	0.2022
<b>Sleep/Energy Domain</b>	18.67	12.56	6.11	[1.42, 10.80]	<b>0.0108*</b>
<b>Overall Quality of Life</b>	10.70	3.49	7.21	[3.42, 11.00]	<b>0.0002*</b>

\* Statistically significant difference versus placebo,  $p \leq 0.05$ .

Note: All scores are re-scaled to 0–100.

BC = bother/concern; SE = sleep/energy

At Month 3, significantly greater improvements were seen with desmopressin compared with placebo based on the total score. The absolute change from baseline due to desmopressin treatment was highly clinically relevant, but also the treatment contrast of approximately 5 in the total score is clinically relevant according to the suggested N-QoL values for clinical improvement.<sup>18, 45, 46</sup> The main driver of the treatment contrast was the sleep/energy domain. The change in the stand-alone overall QoL question was also significant.

### Impact on Quality of Sleep

Clinical benefit was furthermore assessed through three sleep VAS scales included in the diary assessing different dimensions of sleep quality.

For the sleep quality assessments, pooled treatments for all subjects compared changes in key clinical endpoints between responders and non-responders. Two criteria were used to define responders, reduction of  $\geq 2$  nocturnal voids from baseline to Month 3 and Increase of  $\geq 2$  hours in time to first nocturnal void from baseline to Month 3. For both definitions of responders, mean improvement (higher numbers) in sleep quality was statistically significantly greater in subjects from pooled treatment groups who responded than in non-responders. Mean changes in sleep quality (how do you feel right now, rate how refreshed you feel, and quality of sleep last night) are summarized longitudinally in Table 11.

**Table 11: Exploratory Sleep Endpoint Sleep Quality (Longitudinal Analysis – full Analysis Set Responders vs. Non-responders**

Quality of Sleep	Difference in Adjusted Means [ 95% CI ]	P-value
<i>Responder Criteria: ≥2 voids reduction from baseline</i>		
Average of how you feel right now	0.48 [ 0.22; 0.74]	0.0003
Average of how refreshed	0.46 [ 0.20; 0.71]	0.0006
Average of quality of sleep last night	0.69 [ 0.41; 0.97]	<.0001
<i>Responder Criteria: ≥2 hrs increase in time to first void</i>	0.40 [ 0.16; 0.64]	0.0013
Average of how you feel right now	0.31 [ 0.07; 0.56]	0.0109
Average of how refreshed	0.54 [ 0.28; 0.80]	<.0001

Note: Sleep diary questions sleep rank 1-10. Increased score means improved quality of sleep.

### Treatment change in sleep quality

Post-hoc longitudinal analyses (repeated measures ANCOVA adjusting for baseline as a covariate and age stratification factor, treatment, visit, and treatment-by-visit interaction term as factor) were conducted to investigate the treatment effect of desmopressin versus placebo on the change from baseline in the 3 sleep VAS scales. Results are shown in Table 12.

**Table 12: Adjusted treatment differences in mean change from baseline in sleep VAS at Month 3**

	Adjusted Means		Difference in Adjusted Means		
	Desmopressin	Placebo	Treatment contrast	95% CI	p-value
<b>CS41</b>	N=102	N=125			
<b>Mean of Q1: How do you feel right now?</b>	1.21	0.78	0.43	[0.05; 0.82]	<b>0.0265*</b>
<b>Mean of Q2: Rate how refreshed you feel</b>	1.34	0.85	0.49	[0.11; 0.87]	<b>0.0113*</b>
<b>Mean of Q3: Rate the quality of your sleep last night</b>	1.69	1.33	0.36	[-0.03; 0.75]	0.0684

\* Statistically significant difference versus placebo, p≤0.05.

At Month 3, significantly greater improvements were seen with desmopressin compared with placebo in 2 of the 3 sleep VAS scales.

Increasing initial undisturbed sleep time to ≥4 hours is associated with clinically meaningful improvements in sleep quality scores.

## **TOXICOLOGY**

### **(i) Acute Toxicity**

The i.v. acute toxicity of desmopressin acetate was studied in mice, rats and rabbits. Mice tolerated i.v. doses of 2 mg/kg. At doses of 30  $\mu$ g/kg in rats and 50  $\mu$ g/kg in rabbits, only transient changes in clinical behaviour were observed.<sup>12, 13, 41</sup>

### **(ii) Subacute Toxicity**

Results from 14-day studies show that the drug given intravenously to rats at 8  $\mu$ g/kg/day and to rabbits at 6  $\mu$ g/kg/day caused no biologically significant changes in hematological and clinical chemistry parameters. Post-mortem examinations did not reveal any abnormalities.<sup>14, 15</sup>

Rats which received 5 mg/kg/day subcutaneously for 3 days did not show any significant changes in weight, blood count, or organ changes.<sup>41</sup>

### **(iii) Chronic Toxicity**

#### **Subcutaneous Administration**

##### **Rat Studies**

In a controlled 8-week experiment, 20 rats received 2  $\mu$ g/kg/day desmopressin acetate subcutaneously. No increase in blood glucose or morphological or histological pancreatic changes occurred.<sup>42</sup>

Rats (20 per group) which received doses of 5, 50 and 500 ng/kg/day, for six months did not show any significant changes in weight, blood values, or levels of transaminases. The weight of heart, lungs and kidneys decreased in female animals in the lower dose groups but not in the higher ones. In the male animals a decrease in non-esterified fatty acids was noted.<sup>41</sup>

Rats were treated with dose levels of 0.1, 1 and 10  $\mu$ g/kg/day by subcutaneous injection for 13 weeks. Anticipated pharmacological changes were observed in a series of urinary parameters mainly at the high dose: decreased urinary volume and pH; increased specific gravity and concentration of sodium, potassium, chloride and protein. Absolute and relative kidney weights were increased at all dose levels. There were no macroscopic observations at necropsy. Histopathology showed changes at the injection site, where the incidence and severity were slightly increased at the high dose level.

## **Dog Studies**

Dogs (3 per group) which received subcutaneous doses of 10 and 100 ng/kg/day for 6 months did not show any significant changes in comparison with control groups in blood sugar or transaminases and did not show histological or morphological organ changes.<sup>41</sup>

## **Intravenous Administration**

### **Rat Studies**

In rats treated intravenously with desmopressin at dose levels of 9.47, 47.4 or 238 µg/kg/day for 180 days, urinary specific gravity was increased and urinary volume was decreased in all desmopressin treated groups, thus showing the pharmacological effect of the compound. Absolute kidney weight was increased from the mid dose level while body weight related kidney weight was increased from the low dose level. There were no gross pathological changes at necropsy. Histopathological changes were confined to the kidneys and consisted of increased incidence of tubular protein casts from 47.4 µg/kg/day and hyaline droplet degeneration at the high dose level. All changes were reversible after the 30-day reversibility period, except increased kidney weight, which showed incomplete reversibility.<sup>15</sup>

## **Oral Administration**

### **Rat Studies**

Oral administration of desmopressin to rats (20 male and 20 females per group dosed at 25, 75 and 200 µg/kg/day) did not reveal any clinical findings related to desmopressin. Treated male and female rats were comparable to controls with respect to food consumption, body weight gain and water consumption. There were no drug-induced ocular abnormalities.<sup>21</sup>

A dosage-related reduction was seen in levels of total circulating white blood cells, attributable to reduced neutrophil and lymphocyte counts in treated females, when compared with controls, at the week 13 and 26 investigations. Treated males were not affected.<sup>21</sup> Reduced plasma Factor VIII levels were seen in treated females at week 14 and treated males at week 25 in comparison with controls.<sup>21</sup>

The terminal studies revealed no morphological or histological changes related to treatment with desmopressin.<sup>21</sup>

## **Dog Studies**

When desmopressin was given orally to dogs (4 males and 4 females per group, at 0, 25, 75 and 200 µg/kg/day) all animals survived the 26-week period and no clinical signs were observed that were related to treatment. There were no adverse effects on body weight, food and water consumption and no ocular abnormalities. Hematological investigations revealed no treatment-related findings.<sup>16</sup>

During weeks 6, 13 and 26 serum total protein concentrations of treated animals were increased due to an increase in the globulin fraction. However, there were no changes from the pre-dose values in males at 200 µg/kg/day after 13 and 26 weeks treatment and males at 75 µg/kg/day after 26 weeks treatment.<sup>16</sup>

No organ morphological or histological changes were seen on autopsy which could be related to treatment with desmopressin.<sup>16</sup>

## **Reproduction Studies**

### **Subcutaneous Administration**

#### **Rat Studies**

In a teratogenicity study in Wistar rats, neither teratologic nor embryotoxic effects were observed in 369 foetuses from 40 females dosed with up to 50 ng/kg/day desmopressin acetate subcutaneously during day 1 to day 20 of gestation.<sup>40</sup>

#### **Rabbit Studies**

In a study of 78 Dutch belted rabbits which received subcutaneous doses of desmopressin acetate up to 10 µg/kg/day during day 6 and day 18 of pregnancy, neither teratogenic nor embryotoxic effects were observed in 296 fetuses. Weaning was unaffected.<sup>39</sup>

### **Intravenous Administration**

#### **Rat Studies**

A teratology study was performed in rats. Groups of 30 pregnant Slc:Wistar rats were treated daily from day 7 to day 17 of gestation by i.v. administration of desmopressin at dosage levels of 9.47, 47.4 and 238 µg desmopressin/kg/day. A control group received the vehicle, physiological saline. Twenty females in each group were killed on day 20 of gestation to allow fetal examinations; the remaining 10 females were allowed to litter to determine any postnatal effects that might be attributable to prenatal treatment. There were no effects of treatment on the dams, and fetal survival, growth and morphology were also unaffected. Postnatal offspring survival, growth, development, behavior and reproductive performance also showed no effects of prenatal exposure to desmopressin.<sup>22</sup>

### **Genotoxicity**

The genotoxic potential of desmopressin was examined in 3 Ames tests and one mouse lymphoma assay all of which turned out to be negative. Desmopressin is therefore considered to be devoid of mutagenic potential under the condition tested.<sup>22</sup>

### **Carcinogenesis**

Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential.

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**PART III: CONSUMER INFORMATION****NOCDURNA®****Desmopressin orally disintegrating tablets**

This leaflet is part III of a three-part "Product Monograph" published when NOCDURNA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NOCDURNA. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

NOCDURNA is used in the treatment of adults who have to wake up during the night, up to four times, to urinate (pee).

**What it does:**

NOCDURNA contains desmopressin (dez-moe-PRESS-in). It works by making the kidneys reabsorb more water, thereby producing less urine.

**When it should not be used:**

DO NOT take NOCDURNA, if you:

- are allergic to desmopressin acetate or any of the other ingredients in NOCDURNA tablets
- have or have had low blood sodium levels (hyponatremia)
- have a moderate or severe decrease of kidney function  
have heart problems such as heart failure (cardiac insufficiency) and other conditions requiring treatment with water pills (diuretics)
- have a condition known as habitual or psychogenic polydipsia (excessive water drinking)
- have known or suspected syndrome of inappropriate antidiuretic hormone secretion (SIADH) where your body makes too much antidiuretic hormone that may cause too much water to remain in the body resulting in low sodium levels.
- have bleeding problems such as Type II B or platelet-type (pseudo) von Willebrand's disease.
- have conditions which may affect blood sodium such as nausea, vomiting, eating disorders (bulimia or anorexia nervosa), diarrhea, adrenal problems (e.g. Addison's disease), or kidney problems (salt losing nephropathies)

**What the medicinal ingredient is:**

The medicinal ingredient is desmopressin acetate.

**What the nonmedicinal ingredients are:**

The non-medicinal ingredients are gelatin, mannitol and citric acid.

**What dosage forms it comes in:**

NOCDURNA 25 µg is a white, round, orally disintegrating tablet with "25" on one side.

NOCDURNA 50 µg is a white, round, orally disintegrating tablet with "50" on one side.

NOCDURNA comes in a blister pack with each box containing 30 tablets.

The NOCDURNA initiation pack for men over 65 years comes in a blister pack containing 4 tablets.

**WARNINGS AND PRECAUTIONS**

NOCDURNA can cause too much water to remain in the body resulting in low sodium levels (hyponatremia). Hyponatremia is a serious condition which in severe cases and if not treated can result in death. If you experience symptoms such as unusual headache, dark urine or little amount of urine passed, nausea, vomiting, feeling weak or tired, sleepiness, unexplained weight gain, muscle cramps, contact your doctor immediately.

Fluid intake must be reduced to a minimum from 1 hour before taking NOCDURNA until at least 8 hours after taking NOCDURNA to prevent hyponatremia.

**BEFORE you use NOCDURNA talk to your doctor or pharmacist if you:**

- have or have had hyponatremia (low blood sodium levels)
- have constant thirst or the habit of drinking large amounts of water or liquids
- have a fever, the flu, an infection, or diarrhea that may affect your body fluid and salts (electrolytes)
- have any heart disease or high blood pressure
- have kidney problems
- have cystic fibrosis
- have a bladder problem or outlet obstruction
- are pregnant or planning to become pregnant
- are breast-feeding
- have condition that needs to take water pill (diuretic)

Your doctor will ask you to get your blood checked for sodium **before starting NOCDURNA**, and men aged 65 years and older on NOCDURNA 50 µg should have their serum sodium checked **within 4-8 days and after one month after taking NOCDURNA**. These blood tests are for your safety.

NOCDURNA tablets have not been studied in children.

## INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about your other medication, including the ones that you bought without prescription, natural health products. Especially if you are taking any medicines that may increase risk of increased fluid and decreased salt levels such as nonsteroidal anti-inflammatory drugs such as ibuprofen, naproxen, celecoxib (Celebrex).

## PROPER USE OF THIS MEDICATION

You should take NOCDURNA as prescribed by your doctor.

### Usual adult dose:

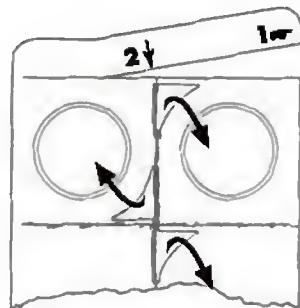
Women: 25 µg once daily at bedtime.  
Men: 50 µg once daily at bedtime

Water or liquid intake must be limited, especially 1 hour before taking NOCDURNA and until at least 8 hours after taking NOCDURNA.

### How to take NOCDURNA?

NOCDURNA should be placed under the tongue one hour before bedtime. The tablet disintegrates instantaneously in the mouth without the need for water.

1. Be sure your hands are dry.
2. Completely remove the end tab of a blister strip by tearing along the perforations, starting from the corner with the hand symbol.
3. Now remove one blister from the strip by tearing along the perforations.
4. Remove the foil on each blister, starting at the corner with the printed arrow, by peeling off the foil in the direction of the arrow. **Do not push the tablet through the foil.**



5. Carefully take one NOCDURNA tablet out of its blister. Place the NOCDURNA tablet under the tongue and allow it to dissolve. Do not chew or swallow the tablet.

### Missed Dose:

If you miss a dose, skip the missed dose and take the next dose at your regular time. Do not take two (2) doses at the same time. Do not make up for a missed dose.

### Overdose:

Do not take more than prescribed for you. In case of drug overdose, contact your doctor, or a poison control centre, or go to emergency room of the hospital near you immediately, even if there are no symptoms

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects with NOCDURNA include:

Common side effects: hyponatremia, dry mouth, diarrhea and headache..

Hyponatremia is a serious side effects with early symptoms include an unusually bad or prolonged headache, confusion, unexplained weight gain, nausea and vomiting, loss of appetite, feeling restless or irritable, feeling weak or tired, sleepiness and muscle cramps. This can become a serious problem and may lead to convulsions and death. If you experience one or more of these symptoms, stop taking this medicine. Tell your doctor immediately or go to the nearest emergency hospital.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptoms / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	hyponatremia (low blood sodium level)		✓	✓
	dry mouth	T		
	headache	T		
	diarrhea	T		

*This is not a complete list of side effects. For any unexpected effects while taking Nocdurna contact your doctor or pharmacist.*

## HOW TO STORE IT

Store at 25°C; excursions permitted to 15 – 30°C. Keep in original package to protect from moisture and light.

### **REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or

- Mail to: Canada Vigilance Program

Health Canada

Postal Locator 0701C

Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance

Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

***NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance program does not provide medical advice.***

### **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals, can be found by contacting the sponsor, Ferring Inc., at: 1-800-263-4057.

This leaflet was prepared by Ferring Inc.

**FERRING**

PHARMACEUTICALS

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